REMARKS

Applicants note with appreciation that the Examiner has withdrawn the previous claim rejections under 35 U.S.C. § 103 in response to the Notice of Panel Decision from Pre-Appeal Review mailed September 4, 2008. However, the Examiner has cited new art to raise new grounds of rejections.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 26-29, 32-34, 63, and 65-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stephenson et al. (BMC Molecular Biology, 12/21/2001, 2(15):1-9) in view of Flanagan et al. (WO 96/26958) and Genentech (WO 00/30673). Applicants respectfully traverse the rejection.

The standard for obviousness under 35 U.S.C. § 103 asks whether the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. An obviousness analysis requires the four factual determinations set forth in *Graham v. John Deere*, 148 USPQ 459 (1966). *See also* MPEP § 2141; *KSR Int'l Co. v. Teleflex Inc,* 82 USPQ2d 1385 (2007). The Examiner has the burden of factually supporting any conclusion of obviousness, which includes findings of objective evidence of a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See* MPEP § 2142. The Court in *KSR* did not disrupt the necessity of the factual inquiry set forth in *Graham*. Further, the Court in *KSR* did not jettison the teaching, motivation, or suggestion test. Rather, the Court clarified that, in circumstances of predictable arts, common sense may provide the requisite teaching, suggestion, or motivation. Further, *KSR* did not alter the basic requirements for establishing a *prima facie* case of obviousness (the references must teach or suggest each and every element of the claimed invention; there must be a suggestion to combine the references; and there must be a reasonable expectation of successfully combining the references to arrive at the claimed invention).

Independent claim 26 recites "an isolated monoclonal antibody which binds to an extracellular domain of an EphB4 protein and promotes apoptosis in a tumor cell, wherein the antibody is selected from bispecific, single-chain, chimeric, human, and humanized antibodies." Applicants emphasize that the claimed EphB4 antibody is clearly functionally defined by its ability to promote apoptosis in a tumor cell.

In this case, Applicants submit that the Examiner has not satisfied the requirement of establishing a *prima facie* case of obviousness. The Examiner concedes that Stephenson et al. do **not** teach: "monoclonal antibodies that specifically bind to an extracellular domain of EphB4 that promote apoptosis in a tumor cell that are selected from bispecific, single-chain, chimeric, human, and humanized antibodies; wherein the antibody inhibits the interaction between Ephrin B2 and EphB4; wherein the antibody inhibits clustering of EphB4; wherein the antibody inhibits phosphorylation of EphB4; said antibodies in a composition comprising a pharmaceutical carrier; cells expressing said antibodies; said antibodies further comprising a label such as a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor; wherein said antibodies inhibit angiogenesis; or wherein the antibodies promote tumor regression." See Office Action, the paragraph bridging pages 4 and 5. However, the Examiner asserts that the deficiencies are made up in the teachings of Flanagan et al. and Genentech et al.

First, Applicants submit that Flanagan et al. and Genentech fail to bridge the gap between Stephenson et al. and the claimed invention. Stephenson et al. disclose a polyclonal EphB4 antibody (H-200). However, Stephenson et al. do **not** teach or suggest a monoclonal EphB4 antibody which promotes apoptosis in a tumor cell.

Flanagan et al. teach the mouse ElF-2 protein, a **ligand** of the Eph receptor (also referred to Ephrin B2), rather than the EphB4 receptor. Specifically, the Examiner asserts that "Flanagan et al further teaches therapeutic antibodies that inhibit binding of ligand to Eph receptors (lines 7-19 on page 20, in particular)." See Office Action, page 5, lines 8-9. Applicants note that the cited section of Flanagan merely teaches that antibodies against the ElF-2 ligand, **not** antibodies against the EphB4 receptor. For example, Flanagan et al. describe that "[a]ntibodies can also be constructed to inhibit the binding of ELF-2 to its Eph receptor . . . since they can be specifically designed to bind to

the extracellular binding domain of **the ligand** and may be utilized for in vivo human therapy" (page 20, lines 7-14, emphasis added). Since Flanagan et al. are directed to a ligand which is entirely distinct from the EphB4 receptor, it is improper and irrelevant to combine Flanagan et al. with Stephenson et al.

Genentech describes that the EphB4 receptor is essential for promoting angiogenic remodeling of primary capillary networks as shown by targeted disruption of the EphB4 gene (e.g., working examples on pages 28-31). Genentech teaches methods of inhibiting angiogenesis and methods of treating diseases or disorders characterized by undesirable or excessive vascularization (e.g., solid malignant tumors), by administering an EphB4 antagonist which includes antibodies (see, e.g., the abstract, and page 2, lines 35-39). However, Genentech does **not** teach an isolated monoclonal antibody which binds to an extracellular domain of an EphB4 protein or an anti-EphB4 antibody which promotes apoptosis in a tumor cell.

Accordingly, the combination of Stephenson et al., Flanagan et al., and Genentech fails to teach all elements of independent claim 26, such as a monoclonal antibody against EphB4 that promotes apoptosis in a tumor cell.

However, the Examiner asserts that "one of skill in the art would recognize that the antibodies taught by the combined teachings above would inhibit clustering of EphB4 and promote apoptosis, as such effects would be found in the antibodies taught by the combined teachings that would sterically hinder clustering and eradicate and reduce tumor size by apoptosis." Office Action, the paragraph bridging pages 7 and 8. The Examiner essentially asserts that the antibody as taught by the combination of Stephenson et al., Flanagan et al., and Genentech would inherently possess the claimed characteristics.

Applicant respectfully disagrees because the legal standard for inherent anticipation is **not met** in this case. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of

circumstances is not sufficient'" (emphasis added). *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Also see MPEP 2112: "[t]he fact that a certain results or characteristics may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)" (emphasis in original).

In this case, the Examiner has not provided any factual basis and/or technical reasoning to reasonably support the assertion that the antibodies disclosed in the cited reference are capable of promoting apoptosis in a tumor cell. It has been well known in the art that antibodies are unpredictable in nature. Indeed, the Board of Appeal noted that: "[h]ybridoma technology is an empirical art in which the routineer is unable to foresee **what particular antibodies** will be produced and which specific surface antigens will be recognized by them (emphasis added)." Ex parte Old, 299 U.S.P.Q. 196, 200 (PTO Bd. App. 1985). One of skill in the art would know that not all antibodies against EphB4 are capable of promoting apoptosis in a tumor cell. Applicants' specification (e.g., pages 102-104 and Figure 59) substantiates the conclusion that hybridoma technology is an empirical art and a skilled artisan is unable to foresee what particular antibodies will be produced. Accordingly, the combination of the cited references fails to inherently teach the antibody as recited in claim 26.

Second, Applicants submit that a skilled artisan would not have had a reasonable expectation of success even if these references were combined, given the state of the art at the time of the invention. As described above, it was well known that antibodies were unpredictable in nature and a skilled artisan was unable to foresee what particular antibodies would be produced (see, e.g., Ex parte Old, *supra*). In view of the unpredictable nature of antibodies, the lack of evidence that EphB4 antibodies could promote apoptosis, and the lack of guidance on how to make and select EphB4 antibodies with a particular feature (e.g., apoptosis-promoting activity), a skilled artisan could not reasonably expect that apoptosis-promoting EphB4 antibodies would be successfully made.

Third, there is no suggestion or motivation for a skilled artisan to make apoptosis-promoting EphB4 monoclonal antibodies as recited in claim 26. Stephenson et al. disclose a polyclonal EphB4 antibody (H-200) purely for detecting expression levels of the EphB4 protein. Although Stephenson et al. speculate that "Eph-ephrin signalling may be important in the progression of colon cancer and that therapies that target this receptor may find application in anti-cancer systems" (page 2, left column), Stephenson et al. **fail** to suggest or teach the use of any antibodies as therapies, let alone any EphB4 monoclonal antibodies which are capable of promoting apoptosis. Rather, Stephenson et al. describe developing agents for reducing EphB4 expression for therapeutic purposes (page 7, left column, under "Conclusions"), thus teaching away from the claimed invention directed to antibodies. Even if a skilled artisan would have been motivated to make EphB4 antibodies as therapeutics, there is no reasonable expectation of success in making the claimed apoptosis-promoting antibodies for the reasons as described above. None of the cited references cure the deficiencies of Stephenson et al.

In view of the above, Applicants submit that independent claim 26 is non-obvious over the cited references. Even if the cited references were combined, the combination still fails to teach each and every limitation of independent claim 26. For the same reasons, all claims depending from claim 26 are a fortiori patentably non-obvious over these cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 26-29, 32-34, 63, and 64-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stephenson et al. (BMC Molecular Biology, 12/21/2001, 2(15):1-9) in view of Flanagan et al. (WO 96/26958) and Genentech (WO 00/30673), and further in view of Sola et al. (Journal of Virology, May 1998, 3762-3772). Applicants respectfully traverse the rejection.

This rejection seems to be direct to dependent claim 64 only. Specifically, the Examiner asserts that "[t]he combined teachings of Stephenson et al, Flanagan et al, and Genentech do not specifically teach a non-human transgenic animal expressing the antibody of claim 26. However, this deficiency is made up in the teachings of Sola et al. Sola et al teaches producing recombinant

monoclonal antibodies in mice (see pages 3767-3768, in particular)." Office Action, page 9, lines 3-7.

Applicants respectfully disagree. As described above, independent claim 26 is not obvious over the combination of Stephenson et al., Flanagan et al. and Genentech. Since claim 64 depends from claim 26 and recites the limitations of claims 26, claims 64 is a fortiori patentably non-obvious over these cited references. The deficiency of these cited references is not made up by the other cited reference (Sola et al.).

In sum, Applicants submit that all of the pending claims are non-obvious over the cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

CONCLUSION

For the foregoing reasons, Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. The Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. **VASG-P01-002.**

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Respectfully submitted,

By _____

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